Chlorine

CAS Registry Number: 7782-50-5

Cl-Cl

I. Physical and Chemical Properties

Description	Yellow/green gas
Molecular formula	Cl_2
Molecular weight	70.096 g/mol
Air concentration conversion	1 ppm = 2.9 mg/m^3 @ 25° C

II. Overview

Chlorine is a direct acting irritant; exposure results in irritation of the respiratory tract, eyes, and skin. There are no direct data indicating that children may be more susceptible to the toxicological effects associated with chlorine than adults. Acute controlled exposure studies in adults to known levels of chlorine have been carried out, while children have been exposed during accidental releases to high, but unknown concentrations. There are no known chronic exposures in children comparable to the long-term occupational exposures to chlorine in adults.

Chlorine may exacerbate asthma since it is a powerful respiratory irritant. As noted in the Introduction in Section III, OEHHA considers asthma to impact children more than adults and thus chemicals that may exacerbate or induce asthma should be considered for listing under SB 25. Since irritants exacerbate asthma, children may be more impacted by chlorine toxicity than adults. In addition, one study (D'Alessandro *et al*., 1996) indicates that adults with hyperresponsive airways (e.g., asthmatics) respond more to chlorine than adults with normal airway responsiveness.

III. Principal Sources of Exposure

In an industrial setting, chlorine is widely used as an oxidizing agent in water treatment and chemical processes. Chlorine is also used to disinfect swimming pool water. Chlorine gas is sometimes used at large public swimming pools, while household pools typically use hypochlorite solutions. Chlorine in the past was used to bleach wood pulp in pulp mills, although chlorine dioxide or ozonation is replacing this use of chlorine. Chlorine as sodium hypochlorite is commonly used as a household cleaner and disinfectant. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 244,955 pounds of chlorine (CARB, 1999). Since 1990 the ARB has monitored for particulate chloride, which includes chloride salts. In 1998, the last year for which complete data have been analyzed, the mean annual statewide concentration of particulate chloride was 1.49 µg/m^3. Ambient chlorine levels are not routinely monitored in California due to reactivity.

IV. Potential for Differential Effects

A. Summary of Key Human Studies

1) Acute exposure / effects in adults

D'Alessandro *et al*. (1996) exposed 10 subjects (age range 18-50), five with and five without airway hyperresponsiveness (HR), to 1.0 ppm chlorine for 1 hour by mouth-breathing facial mask. In addition, the five people with the HR were exposed to 0.4 ppm chlorine. After inhalation of 1.0 ppm, FEV_1 immediately fell significantly in both types of subjects; the decrease was greater among the HR subjects compared with the normals ($p = 0.04$). Specific airway resistance (SR_{aw}) increased more among the HR group compared with normals ($p = 0.04$). Among all 10 people, the proportional change in FEV_1 after exposure to 1.0 ppm chlorine correlated with baseline reactivity (Spearman rank correlation (r) = 0.64, $p < 0.05$). No significant chlorine-related pulmonary function deficits persisted 24 hours after exposure. Exposure of the 5 persons with HR to 0.4 ppm chlorine did not significantly affect pulmonary function. The authors concluded that persons with hyperreactive airways show a clinically significant, exaggerated airway response to 1.0 ppm chlorine, but not 0.4 ppm.

Rotman *et al*. (1983) studied clinically significant changes in pulmonary function tests (PFTs) following controlled chlorine exposures. Using a group of 9 volunteers (8 normal volunteers (ages 19-33) plus 1 volunteer with allergic rhinitis), data were collected on several PFTs following 4- and 8-hour exposures to 0, 0.5, and 1.0 ppm (0, 1.45, and 2.9 mg/m^3) chlorine. The subject with allergic rhinitis was excluded from the final group mean statistical analysis due to the severity of his response to chlorine exposure. Although 8-hour exposure to 1 ppm chlorine resulted in clinically significant decreases in FEV_1 (4 subjects) and clinically significant increases in specific airway resistance (SR_{aw}) (4 subjects), there were no reports of respiratory distress among the normal subjects (Rotman *et al*., 1983). The one subject with allergic rhinitis developed shortness of breath and wheezing following a 4-hour exposure to 1 ppm chlorine and left the exposure chamber (Rotman *et al*., 1983). Pulmonary function tests showed that this subject had a clinically significant increase in pulmonary SR_{aw} and a clinically significant decrease in FEV_1 when compared to sham exposure of 8 healthy subjects and when compared to the subject's own sham control values. The subject also had compromised lung function relative to the 8 healthy subjects during sham exposures. The pulmonary tests under sham control conditions also showed that exposure of the sensitive subject to 0.5 ppm chlorine for 8 hours, but not 4 hours, resulted in a clinically significant, greater than 100% increase in SR_{aw} and clinically significant, greater than 20% decrease in FEV_1. However, no clinical symptoms in the sensitive individual and no apparent indication of bronchoconstriction were reported at 0.5 ppm.

A concentration- and time-dependent severity of irritation to the eyes and throat was shown by exposure of "up to" 29 volunteer subjects (ages 20-33) to chlorine (Anglen, 1981). Volunteers were exposed for 4 or 8 hours to 0, 0.5, 1.0, and 2.0 (4 hour exposures only) ppm chlorine. Severity of irritation was subjectively measured by questionnaires from the subjects every 15-60 minutes, and was

divided into 5 categories, which ranged from barely perceptible to clearly objectionable. A statistically significant decrease in mean FEV_1 (−15.3%) for the group was observed following 8-hour exposure to 1.0 ppm chlorine. A consistent, statistically significant increase in throat irritation in subjects exposed to 1.0 ppm chlorine began at 1 hour into exposure. A NOAEL of 1 ppm was determined for a 30 minute exposure where no effects were reported. Consistent throat irritation was not observed in subjects during a 4-hour exposure to 0.5 ppm. However, 0.5 ppm chlorine produced throat irritation and an urge to cough after a 4-hour exposure.

Two earlier human studies suggest that some test subjects develop respiratory distress at concentrations of chlorine similar to that in Rotman *et al*. (1983). Rupp and Henschler (1967) gradually increased the concentration of chlorine was from 0 to 1.3 ppm over a 50 minute period. One subject developed shortness of breath and a severe headache following exposure to 1.0 to 1.3 ppm chlorine for 35 to 50 minutes. NIOSH (1976) suggested that this subject was sensitive to the irritant effects of chlorine. In a study by Beck (1959), one subject (out of 10) judged a 20 minute exposure to 1 ppm chlorine as unbearable due to sensory skin and conjunctival irritation, headache, and slight respiratory distress. It was not indicated in the study if this was a "sensitive" individual and it was unclear if clinical symptoms indicative of bronchoconstriction had actually occurred.

In a human poisoning case, a 20 year old male with a questionable history of asthma was exposed to 0.05 ounce/1,000 ft^3 ($^1/_{20}$ ounce per 1,000 cubic feet (equivalent to 19 ppm)) of chlorine for several minutes (Monto and Woodall, 1944). Immediately following exposure, the patient did not complain of any unusual irritation or shortness of breath. Several hours later, however, the subject was hospitalized with dyspnea and wheezing, with rales over the chest area. The diagnosis was pulmonary edema. The patient's past history included one questionable asthmatic attack in which he was subsequently told that he was sensitive to dust.

2) Acute exposure/effects in children

Children have been exposed to chlorine gas from leaking tanks while they were in swimming pools. In none of the exposure incidents in children was the exposure concentration measured or estimated. Thus it is difficult to compare effects with acute adult exposures to known concentrations of chlorine.

Decker (1988) reported that children exposed to chlorine gas had acute respiratory distress and eye irritation. Wood *et al*. (1987) reported that two boys, 3- and 7-years old, exposed to a high concentration of chlorine gas, had acute respiratory effects and were hospitalized. Sexton and Pronchik (1998) studied 13 children aged 6-18 years exposed by inhalation to chlorine gas at two community swimming pools. The patients had eye and throat irritation, chest pain, anxiety, shortness of breath, wheezing, and chest tightness, and most had occasional expiratory wheezing. Five children were admitted to the hospital due to hypoxia; four of these also had mild carbon dioxide retention.

Pulmonary function tests (PFT) were performed on 84 children (ages 9-17) from a school, near a plant manufacturing chemicals in Chembur, a suburb of Bombay, from which large amounts of chlorine gas leaked out two weeks previously (Pherwani *et al*., 1989). Only 20 had normal PFTs; 56 (66.7%)

showed an obstructive pattern and 8 (9.5%) showed a restrictive pattern of PFTs. The lower PFTs might be due to the incident, but the children also live in a polluted area of Bombay and a second incident occurred during the PFT administration.

3) Acute exposure/effects simultaneously in children and adults.

During an accident caused by a malfunction of the water chlorinating system in a community pool in Rome in 1998, 282 people, including 134 children under 14, inhaled hydrogen chloride and sodium hypochlorite and their reaction products (Agabiti *et al*., 2001). Acute respiratory symptoms occurred among 66.7% of adults and 71.6% of children. The incidences were highest among those who had chronic respiratory disease and had a longer duration of exposure. In about 30%, respiratory symptoms persisted for 15-30 days. Both in children and in adults, lung function levels were lower in those who reported a high intensity of exposure.

4) Exposure/effects in competitive swimmers.

An interesting subset of people exposed to chlorine is competitive swimmers and other young people in swimming pools, especially enclosed ones. Measurements of the chlorine concentration at the breathing level of swimmers (< 10 cm) obtained randomly during five nonconsecutive days in four different enclosed swimming pools in Spain yielded a mean chlorine level in all the pools of 0.42 ± 0.24 mg/m^3 (Drobnic *et al*., 1996). The authors noted that the mean value is below the TLV of 1.45 mg/m^3 (0.5 ppm) for an eight-hour workday. However, they estimate that a swimmer might inhale 4-6 g chlorine in a daily training session of 2 h, while a worker would inhale 4-7 g in 8 hours if working at the TLV.

Competitive swimming often starts early, at age 6 or so. Competitive swimmers inhale and "microaspirate" large amounts of air that floats above the water surface, which means exposure to chlorine and to chlorine derivatives from swimming pool disinfectants. The risk of asthma is especially increased among competitive swimmers, of which 36% to 79% show bronchial hyperresponsiveness to methacholine or histamine (Helenius and Haahtela, 2000). Mild eosinophilic airway inflammation is often seen.

B. Summary of the Key Animal Studies

In order to develop an animal model of the asthma-like abnormality known as reactive airways dysfunction syndrome (RADS; acute, irritant-induced asthma), Demnati *et al*. (1995) evaluated the effects of chlorine exposure on airway mucosa and lung parenchyma. Seventy-four Sprague-Dawley rats were exposed to air (controls) or to 50, 100, 200, 500, and 1,500 ppm of chlorine for 2 to 10 minutes. Exposure to 500 ppm did not induce significant histological changes. Exposure to 1,500 ppm for 2 minutes induced perivascular edema and the appearance of focal mild inflammation. Exposure to 1,500 ppm for 10 minutes caused profound histological changes. These included (1) airspace and interstitial edema associated with bronchial epithelial sloughing at 1 hour; (2) decreased edema and the

appearance of mucosal polymorphonuclear leukocytes at 6 to 24 hours (maximal at 12 hours); and (3) epithelial regeneration, manifested by hyperplasia and goblet cell metaplasia, at 72 hours.

Winternitz *et al*. (1920) reported severe lung edema and desquamation of the trachea and bronchial epithelium in dogs exposed to chlorine gas at lethal concentrations (concentration not reported). Bronchial constriction from the irritant properties was noted.

V. Additional Information

A. Other Toxicity

Exposure to 3-6 ppm (9-17 mg/m³) chlorine results in stinging or burning sensations from irritation and corrosion of mucous membranes including the eyes, skin, and the respiratory system (Baxter *et al*., 1989; Wither and Lees, 1985). At high concentrations, inhalation may result in necrosis of the tracheal and bronchial epithelium as well as in pulmonary edema. Delayed pulmonary edema may also develop up to 24 hours following acute exposure. Death at high exposure (400-1000 ppm) is mainly from respiratory failure or cardiac arrest due to toxic pulmonary edema. Bronchopneumonia may be a common and potentially lethal complication of pulmonary edema.

Shi (1990) evaluated workers (age range = 23-52 years) from a plant producing chlorine using diaphragm cells who were exposed to a range of 2.60-11.0 mg/m^3 (0.37-1.75 ppm) chlorine. Increased upper airway complaints and significant decrements in lung function were noted in chlorine-exposed workers.

Kennedy *et al*. (1991) compared pulp mill workers (including some exposed to chlorine or chlorine dioxide "gassings") to an unexposed control group of rail yard workers and found a significantly higher prevalence of wheezing in pulp mill workers (both smokers and nonsmokers) who had reported more than one episode of chlorine "gassing." The data suggested that chronic respiratory health impairment is associated with exposure to chlorine and/or chlorine dioxide.

In a study of Quebec pulp mill workers Bherer *et al*. (1994) found a 91% incidence of respiratory symptoms in workers who had experienced high accidental exposures. Twenty-three percent of the 58 workers still experienced bronchial obstruction and 41% continued to have bronchial hyper-responsiveness. Lower baseline FEV_1 was seen in those with a lower PC_{20}, and 52% of these workers showed an FEV_1 < 80% predicted. Thus high chlorine exposure can result in Reactive Airways Dysfunction Syndrome (RADS).

Ventilation was affected by chlorine inhalation, as indicated by a decrease in the maximal midexpiratory flow (MMF) in chlorine gas workers exposed to <1 ppm Cl_2 with occasional excursions (Chester *et al*., 1969).

Exposure of rats and mice to 9-11 ppm chlorine for 6 hours produced severe lesions in specific locations in both olfactory and respiratory epithelia of the nasal passages with a widespread loss of cilia (Jiang *et al*., 1983).

Wolf *et al*. (1995) exposed male and female B6C3F1 mice and F344 rats (70 per group, 280 per sex per species) to chlorine gas at 0 ppm, 0.4 ppm, 1.0 ppm, and 2.5 ppm intermittently for 2 years. Exposure began when the animals were 55 days old. Statistically significant damage to olfactory epithelium occurred in all exposed rats and female mice and also in the 1.0 and 2.5 ppm exposed groups of male mice. A LOAEL of 0.4 ppm was determined for upper respiratory epithelial lesions.

Klonne *et al*. (1987) exposed 32 male and female rhesus monkeys to chlorine gas 6 hours/day, 5 days/week for one year to 0, 0.1, 0.5, and 2.3 ppm Cl_2. The animals have a 35-year life-span and were exposed while they were still growing. Pulmonary function evaluations yielded a statistically significant trend for increasing pulmonary diffusing capacity and distribution of ventilation values for males and females in the 2.3 ppm exposure group. Both males and females exhibited significantly increased respiratory epithelial hyperplasia at 2.3 ppm. A mild form of the lesions was also seen at 0.5 ppm, 0.1 ppm (females only), and in one control male.

B. Regulatory Background

Chlorine is a federal hazardous air pollutant (HAP) and was identified as a toxic air contaminant (TAC) in California in April 1993 under AB 2728.

OEHHA Health Guidance Values

Acute Reference Exposure Level (REL)	210 µg/m^3 (0.07 ppm)
Chronic Reference Exposure Level (REL)	0.2 µg/m^3 (0.08 ppb)
Cancer Potency	Not known to be carcinogenic
Proposition 65	Not listed

OEHHA (1999) adopted an acute Reference Exposure Level (REL) for chlorine of 0.07 ppm (210 µg/m³) based on a NOAEL of 1 ppm for a 30 minute exposure (Anglen, 1981). OEHHA (2000) adopted a chronic REL for chlorine of 0.08 ppb (0.20 µg/m^3) based on a Benchmark Concentration (BMC_{05}) of 0.14 ppm determined for rats (Wolf *et al*., 1995).

VI. Conclusions

Chlorine is a respiratory irritant that may exacerbate asthma. D'Alessandro *et al*. (1996) showed that people with hyperreactive airways were more affected by 1.0 ppm chlorine than non-hyperreactives, but this difference was not noted at 0.4 ppm. General ambient exposures are very small and most chlorine exposures occur after accidental releases. Due to limited evidence of a differential effect and low potential for exposure, OEHHA placed chlorine in Tier 2.

VII. References

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